

Appl No. 09/646,984  
Amdt. Dated August 20, 2003  
Reply to Office Action of May 20, 2003  
Customer No. 27752

### Remarks

Claims 1, 2, 11-16, 18, 20-22, 24, 26, and 27 are pending in the present application. No additional claims fee is due. Claims 1, 12-14, and 24 have been amended. Support for the amendment to Claims 1, 12-14, and 24 can be found at least on page 5 of the specification.

### Response to the Office Action

#### The Rejection under 35 U.S.C. 112, second paragraph

Claims 1, 2, 11-16, 18, 20-22, 24, 26, and 27 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite. Specifically, claims 1 and 12-14 have been rejected as being incomplete. In response, Applicants have amended claims 1, 12-14, and 24 as suggested by the Examiner. Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. 112, second paragraph has been overcome.

#### The Rejection under 35 U.S.C. 103(a) over Bryan et al.

Claims 1, 2, 11-20, 22, 23, and 27 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Bryan et al. (US 5,567,601). Applicants respectfully traverse this rejection, as there is no suggestion or motivation to modify the reference, as required by MPEP 2143.01. Bryan et al. teach the deletion of amino acids at the 70-74  $\alpha$ -helix *together with the deletions of amino acids corresponding to amino acid positions 75-83* of the subtilisin BPN'. The present invention teaches deletion of one or more of positions 70-84 corresponding to subtilisin BPN', *wherein the deletion is not 75-83*. Therefore, a *prima facie* case of obviousness has not been established.

The Office Action states that it would have been obvious to delete fewer of the amino acids among the positions corresponding to positions 75-83 of subtilisin BPN' or to add further deletions to the most preferred deletion at the positions corresponding to positions 70-74 of subtilisin BPN'. The Office Action also states that the lack of specific examples of the deletions taught by Bryan et al. does not detract from the ability of their teachings to motivate one of ordinary skill in the art to make further deletions. However, the mere fact that the prior art could be modified would not have made the modification obvious unless the prior art suggested the desirability of the modification, *In re Mills* 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990); *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992). There is no such motivation in Bryan et al. Bryan et al. only briefly mention a deletion of any amino acid only at positions 75-83, all other aspects of the invention specify a deletion in combination with the preferred deletion of 75-83. Applicants' specification and claims describe which deletion positions are preferred, and none of them include a deletion of 75-83. It would not have been obvious to delete positions other than the most preferred deletions of Bryan et al. because Bryan et al. effectively taught away from such

Appl No. 09/646,984

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Customer No. 27752

independent deletions by citing only examples with the deletions of positions 75-83. Column 9 and Table I describe specific mutants synthesized by Bryan et al., and all of the examples indicate that a deletion must be accompanied by the most preferred deletion of amino acids at positions 75-83. While a deletion of positions 70-74 of the  $\alpha$ -helix position may improve stability of the enzyme, it does so in combination with the preferred deletion of positions 75-83.

Obviousness can only be established by modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art (MPEP 2143.01). Bryan et al. provides no motivation to make deletions other than those including positions 75-83, and therefore never explicitly or implicitly suggest that their invention can be modified to create the present invention. Therefore, it would not have been obvious to create a subtilisin of the present invention, as Bryan et al. does not teach or suggest a deletion independent of a deletion of positions 75-83.

Furthermore, Applicants respectfully traverse this rejection, as there would be no motivation to modify the Bryan et al. teaching of subtilisin stability to the present invention's teaching of immune surveillance. Bryan et al. teach highly stable subtilisins that are independent of calcium, and therefore are more stable in the presence of metal chelators commonly found in industrial environments. The present invention teaches redesign of subtilisins to alleviate the immunogenic properties of an epitope region, thereby decreasing the immunological response. Thus, Bryan et al. teach protecting the protease from metal chelators, and the present invention teaches protecting the protease from a foreign immune system. The issues of subtilisin stability and immune surveillance are completely separate problems. One skilled in the art would have no motivation to modify Bryan's teachings of altering amino acids for the purpose of increasing subtilisin stability and result in the present invention's teachings of redesigning subtilisins to alleviate the immunogenic properties that cause immunological responses.

While both Bryan et al. and the present invention teach protection of the protein, the mechanisms in achieving the protection are clearly different and therefore, one of ordinary skill in the art would not have been motivated to modify the Bryan et al. reference. One skilled in the art interested in the teachings of Bryan et al. would be focused on protecting the protease from high concentrations of metal chelators. Bryan et al. disclose a method of modifying serine protease enzymes to eliminate calcium binding in order to create mutated subtilisin enzymes that are more stable in the presence of metal chelators. Bryan et al. do not teach that this method could be enhanced or applicable to any other form of protease protection. Therefore, one skilled in the art would have no motivation to modify the teachings of Bryan et al. to create subtilisins that evoke a decreased immunological response.

Appl No. 09/646,984  
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Thus, the obviousness rejection given in the Office Action does not establish a *prima facie* case of obviousness. Therefore, Applicants contend that the claimed invention is unobvious and that the rejection should be withdrawn.

*The Rejection under 35 U.S.C. 103(a) over Bryan et al. and Powell et al.*

Claims 24 and 26 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Bryan et al. and Powell et al. (US 6,060,546). Applicants respectfully traverse this rejection because there is no motivation to combine the references, as required in MPEP 2143.01.

There is no motivation to combine Bryan et al. with Powell et al.. Powell et al. only teach the preparation of a personal care composition comprising subtilisin SP 544, while Bryan et al. specifically teach subtilisin deletion and modification. One skilled in the art would not be motivated to combine a reference teaching specific deletions and modifications of specific regions of different subtilisins with the Powell et al. general description of a personal care composition comprising subtilisin SP 544. Bryan et al. specifically teach altering amino acids in subtilisin BPN' to increase stability with metal chelators. Powell et al. teach that subtilisins can be used in personal care compositions, and there would be no motivation to combine that broad and general teaching with a reference teaching inhibition of proteolysis in an industrial environment.

Therefore, Applicants contend that a *prima facie* case of obviousness has not been established, and the claimed invention is not obvious in view of the cited references.

*The Rejection under 35 U.S.C. 103(a) over Bryan et al. and Arbige et al.*

Claim 21 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Bryan et al. and Arbige et al. (EP 0 260 105). Applicants respectfully traverse this rejection because there is no motivation to combine the references, as required in MPEP 2143.01.

There is no motivation to combine Bryan et al. with Arbige et al.. Arbige et al. teach modifying enzymes with catalytic triads in order to alter the transesterification rate/hydrolysis rate ratio when the enzymes are used as a catalyst, while Bryan et al. teach subtilisin deletion and modification related to increasing stability in the presence of metal chelators. One skilled in the art would not be motivated to combine a reference teaching modification related to increasing stability with the Arbige et al. description of altering the transesterification rate/hydrolysis rate ratio. Bryan et al. specifically teach altering amino acids in subtilisin BPN' to increase stability with metal chelators. Arbige et al. teach that enzymes act as a catalyst by creating competing types of reactions including hydrolysis (acting on an ester form an alcohol and an acid) or transesterification (replace the ester with a different ester). There would be no motivation to combine the Arbige et al. teaching of alteration of nucleophile specificity in order to improve the use of enzymes in synthetic reactions with a reference teaching inhibition of proteolysis in an industrial environment.

Appl No. 09/646,984

Amdt. Dated August 20, 2003

Reply to Office Action of May 20, 2003

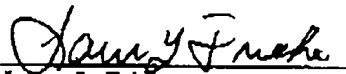
Customer No. 27752

Therefore, Applicants contend that a *prima facie* case of obviousness has not been established, and the claimed invention is not obvious in view of the cited references.

**Conclusion**

Applicants have made an earnest effort to place their application in proper form and to distinguish the invention as now claimed from the applied references. WHEREFORE, Applicants respectfully request reconsideration of this application, entry of the amendments presented herein and allowance of Claims 1, 2, 11-16, 18, 20-22, 24, 26, and 27.

Respectfully submitted,  
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Customer No. 27752